Prevalence and Incidence of Atrial Fibrillation in Ambulatory Patients with Heart Failure

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Short title: atrial fibrillation in patients with heart failure

Abstract

Heart failure (HF) and atrial fibrillation (AF) commonly co-exist. We aimed to determine the prevalence and incidence of AF in ambulatory patients with HF. HF was defined by the presence of symptoms or signs supported by objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) ≤45% (HFrEF), or LVEF >45% and a raised plasma concentration of amino-terminal pro-B type natriuretic peptide (NT-proBNP>220ng/L; HFpEF). Of 3,570 patients with HF, 1,164 were in AF at baseline (33%), with a higher prevalence among patients with HFpEF compared to HFrEF (40% vs 26%, respectively, p<0.001). Compared to patients with HF in sinus rhythm (SR), those in AF were older, had more severe symptoms and higher NT-proBNP, worse renal function and were more likely to receive loop diuretics, despite having a higher LVEF. Of those in SR, 1,372 patients had HFrEF and 1,034 had HFpEF. The incidence of AF at one year (3.0%) was similar for each phenotype (p=0.73). Increasing age, male sex, history of paroxysmal AF and higher plasma concentrations of NT-proBNP were independent predictors of incident AF during a median follow-up of 1,574 (IQR: 749-2,821) days; the predictors were similar for each phenotype. In conclusion, the prevalence of AF is high, especially in patients with HFpEF, but its incidence is modest. This may be because their onset is near simultaneous with the development of AF precipitating the onset of HF.

Keywords: atrial fibrillation, heart failure, prevalence, incidence, NT-proBNP**.**

Background

Heart failure (HF) and atrial fibrillation (AF) are common, both associated with an increase in morbidity and mortality (1, 2), and share many of the same predisposing conditions, such as increasing age, hypertension, diabetes and ischaemic heart disease (3, 4).

Pathophysiologically, HF and AF are closely intertwined. A constant and prolonged increase in atrial pressure might increase atrial wall fibrosis, impair atrial contraction, and provoke AF in patients with, or predisposed to, HF. In turn, the onset of AF may cause a fast ventricular rate, or a fall in the atrial contribution to ventricular filling, with a subsequent fall in cardiac output, leading to worsening of pre-existing, subclinical, ventricular dysfunction and, ultimately, the new-onset or clinical worsening of HF (5).

The prevalence of AF in patients with heart failure and a reduced ejection fraction (HFrEF) enrolled in registries or clinical trials is high, ranging from 15% to 40% (6-12). It may be even higher (13-15) in patients with HF and preserved left ventricular ejection fraction (HFpEF), perhaps reflecting their older age. However, there are few data on the *incidence* of new-onset AF in patients with HF, which may be no higher than 5%/year (4, 16). Our aim was to determine the prevalence and incidence of AF in ambulatory patients with heart failure and the clinical predictors of new-onset AF.

Methods

Between 2001 and 2014, a large, epidemiologically representative cohort of patients with suspected heart failure has been enrolled at a single NHS community heart failure clinic serving a local population of about 600,000 people (The Hull LifeLab). Referrals to the heart failure clinic include a broad range of patients from both primary and secondary care

physicians. Patients are consented for the use of medical information prior to investigation. Some patients had no prior diagnosis of heart failure and were treatment naive, therefore requiring initiation of guideline-recommended treatment, or might have a pre-existing diagnosis of heart failure and already have been initiated on treatment that might require optimisation.

Patients are reviewed by heart failure specialist nurses and doctors and are followed up at regular intervals, usually at 4 months, 12 months, and then yearly unless a clinical appointment is requested sooner by the patient, other physicians or a specialist nurse. Patients who develop new, or worsening symptoms, are encouraged to contact the department and are followed more closely if needed. Information on demography, symptoms & signs, haematology and biochemistry profiles (including amino-terminal pro-brain natriuretic peptide (NT-proBNP)), and echocardiograms are systematically recorded at each time point in a dedicated electronic health record stored on a secure NHS server.

Electrocardiography was systematically performed at each clinic visit to document heart rate and rhythm, and QRS duration. If clinically indicated, we investigated for symptoms of palpitations using ambulatory cardiac monitoring. Titration of treatment is coordinated by the clinic but often implemented by community heart failure nurses or general practitioners.

For the purpose of the present analysis, HF was defined by the presence of symptoms or signs of HF supported by objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) $\leq$45% or equal to, or worse than mild to moderate left ventricular systolic dysfunction (LVSD) on visual assessment at echocardiography (HFrEF), or raised plasma concentration of amino-terminal pro-B type natriuretic peptide (NT-proBNP) >220 ng/L) consistent with the European Society of Cardiology (ESC) consensus statement for diagnosis of HFpEF at the time of initiation of the study (17). Patients who did not fulfil criteria

for cardiac dysfunction (those with LVEF >45% or equal to, or better than, mild LVSD at visual assessment at echocardiography who had an NT-proBNP below or equal to 220 ng/l) were used as a control group.

In 2016, the ESC-HF guidelines changed the definition for heart failure (18), after our analysis plan was developed. The new guidance suggested taking a cut-off of LVEF<40% as the upper limit for making a diagnosis of HFrEF; and reduced the NT-proBNP cut-off in excluding heart failure to 125 ng/L. Therefore, we partially repeated our analysis applying the newer ESC-HF 2016 criteria, defining HF by the presence of symptoms or signs supported by objective evidence of cardiac dysfunction: either LVEF <40% or equal to, or worse than moderate LVSD on visual assessment on echocardiography (HFrEF), or raised plasma concentration of NT-proBNP (>125 ng/L; HFpEF, without further distinguishing between those with mid-range (HFmrEF) or preserved ejection fraction).

Patients whose echocardiography, ECG or NT-proBNP (in the presence of normal or mildly reduced LVEF) were not available at baseline have been excluded from this analysis (n=511; supplementary figure 1).

For patients in sinus rhythm at baseline, information regarding previous episodes of paroxysmal atrial fibrillation was retrieved from the electronic hospital records and hospital or General Practitioner (GP) notes before their baseline visit. We did not attempt to distinguish between persistent and permanent AF.

Ischaemic heart disease (IHD) was defined as a previous documented history of myocardial infarction. Diabetes mellitus (DM) was defined as previous medical history of DM based on GP or hospital records or on the prescription of treatment for DM. Hypertension (HTN) was defined as previous medical history of HTN based on GP or

hospital records, or systolic blood pressure ≥160 mmHg or diastolic ≥100 mmHg at the baseline clinical visit, despite the use of medications that might decrease systolic or diastolic blood pressure (including beta-blockers, ACE-inhibitors or sartans, thiazide-like diuretics, and calcium-antagonists). Valvular heart disease was defined as a significant valvular abnormality identified as one of the causes for the referral or by baseline echocardiography, or a previous history of aortic or mitral valve replacement. Peripheral vascular disease (PVD) was defined as previous documented history of PVD, including abdominal aortic aneurysm, from GP or hospital records.

Our hospital is the only hospital providing acute medical care for the region and is notified of all acute clinical events. It is unusual, although possible, for a patient with heart failure followed-up in our region to be admitted elsewhere. For patients who move out of the region, other clinical information, in particular death, can be tracked through hospital health records.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All participants gave their written informed consent.

Categorical data are presented as numbers and percentages; normally distributed continuous data as mean ± SD and non-normally distributed continuous variables as median and interquartile range. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test for categorical variables. Cox proportional hazard regression models were used to investigate the relationship of variables and incident AF in the overall population, and separately in patients with HFrEF and HFpEF. Models were constructed including and excluding left atrial diameter, available in <90% of patients. Treatment variables were not

included in either model as these might be confounded by indication and might vary over time. Assumptions of the models, such as multicolinearity and proportional hazards, were tested. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome. All analyses were performed using SPSS (v.22) and Stata software. A 2-sided p-value < 0.05 was considered statistically significant.

Results

Of the 5,211 patients with available data, 511 were excluded due to missing information (Figure 1 supplementary), leaving a total of 4,700 patients in the study. Of these, 3,570 met the definition of heart failure and 1,130 did not (Table 1 supplementary).

Of those with heart failure, 1,164 (33%) had AF on their baseline electrocardiogram. AF was more common in patients with HFpEF than HFrEF (40% vs 26%, respectively, p<0.001). Compared to patients in SR, those with AF and HF were older, had more severe symptoms, lower systolic blood pressure and more commonly had a clinical history of TIA/stroke and valvular heart disease. They also had higher plasma concentrations of NT-proBNP, worse renal function and were receiving more loop diuretics; on echocardiography, they had larger left atrial diameters, despite having a higher LVEF (Table 1).

Compared to those with HFrEF and AF, those with HFpEF and AF were older and more likely to be women, had higher BMI and systolic blood pressure, better renal function, but lower haemoglobin. They also had fewer symptoms, a smaller left atrium, were less likely to be taking loop diuretics and had lower plasma NT-proBNP (supplementary table 2).

During a median follow up of 1,624 (784-3054) days, 1,962 (42%) patients with HF died. The presence of AF was associated with higher mortality (hazard ratio (HR) vs those in sinus rhythm: 1.33, 95% CI 1.20-1.47, p<0.001). Patients with HFrEF and AF had the worst outcome (HR: 1.19, 95% CI 1.02-1.41, p=0.026 vs those with HFpEF and AF, figure 1 unadjusted; adjusted for age and sex, figure 2 supplementary).

Compared to patients with HFrEF in SR (n = 1,372), those with HFpEF in SR (n = 1,034) were older, had less severe symptoms, were more likely to be women, to have hypertension or valvular disease, but less likely to have ischaemic heart disease (Table 1). They had lower NT-proBNP and haemoglobin concentrations, smaller left atria, better renal function, and were less frequently treated with loop diuretics.

For those who had a minimum of 1 year follow-up, there was no difference in the incidence of persistent AF at 1 year between patients with HFrEF (n=34 of 1,195; 2.8%) and those with HFpEF (n=28 of 901; 3.1%; p=0.73).

In univariable analysis, ischaemic heart disease, lower systolic and diastolic blood pressure, and higher creatinine and bilirubin were associated with incident AF (table 2). In a multivariable analysis that did not include left atrial diameter, only greater age, male sex, history of paroxysmal AF and higher NT-proBNP were independent predictors of incident AF. When LA diameter was entered into the model, the diagnosis of HFrEF rather than HFpEF and LA diameter were also independently associated with incident AF (table 2).

For patients with HFrEF, increasing age, male sex, greater LogNT-proBNP and history of paroxysmal AF independently predicted incident AF (supplementary table 3).

In multivariable models for patients with HFpEF, greater Log NT-proBNP, male sex, and history of paroxysmal AF predicted incident AF. When LA diameter was added, it competed with male sex for the association with incident AF (supplementary table 4).

Compared with the patients in the lowest quintile of NT-proBNP, those in the highest quintiles had 3 to 4 -fold greater risk of developing AF during follow-up (Table 3).

Applying newer ESC-HF criteria, the number of patients with HF increased from 3,570 to 3,890, of whom 1,372 had HFrEF and 2,518 had HFpEF. Compared to patients with HFpEF, those with HFrEF were younger (71 (63-78) vs 75 (69-81) years; p<0.001), had higher plasma NT-proBNP (1819 (787-4028) vs 750 (296-1757) ng/l; p<0.001) and creatinine (105 (88-131) vs 96 (80-122) μmol/l: p<0.001), and a larger left atrial diameter (4.4 (3.9-4.9) vs 4.1 (3.6-4.6) cm, p<0.001).

Of 1166 patients with HF and AF at baseline (30%), the prevalence was greater amongst patients with HFpEF (33%) compared to HFrEF (25%; p<0.001).

Of those in SR (n=2724), 2,467 had at least one-year follow-up. The incidence of persistent AF at one year was 2.6% and was similar in patients with HFrEF (23 of 928 patients; 2.5%) and HFpEF (40 of 1,539 patients; 2.6%; p=0.85). Changing the definition of heart failure did not change predictors of incident AF (Table 5 supplementary).

Discussion

We previously reported the low incidence of AF in a cohort of 623 patients with HFrEF and sinus rhythm. Here, we expand the numbers of patients and include many more with HFpEF on echocardiography (19). Our results show that in ambulatory patients with heart failure, the prevalence of atrial fibrillation is high, particularly in those with HFpEF, but its incidence is fairly low, which is most readily explained by concurrent onset of HF and AF. Similar observations have been made both from the Framingham study (4, 20) and Olmsted County residents (15). AF may often be the precipitating cause of clinically overt HF but pre-existing ventricular dysfunction is likely to contribute both to the development AF and to a reduction in cardiac reserve, making the patient more vulnerable to the onset of HF.

Our findings confirm the association between well-known risk factors and incident AF, which maintain their clinical importance regardless of left ventricular phenotype. We found that incident AF is more common in older individuals and men, perhaps reflecting an association with ischaemic heart disease.

Raised plasma concentrations of natriuretic peptides are associated with an increasing risk of developing AF in the general population and in individuals at increased cardiovascular risk, but little is known about the association of natriuretic peptides with incident AF in ambulatory patients with HF, particularly in those with HFpEF. We found a linear increase in the risk of developing AF with increasing plasma concentrations of NT-proBNP regardless of left ventricular phenotype.

In almost 4,000 participants in the Cardiovascular Health Study aged older than 65 years and free of AF, of whom only 3% had HF, those in the highest quintile of baseline NT-proBNP had a 5.2 fold greater risk of developing AF during follow-up compared with the

lowest quintile (21). In a report including more than 26,000 individuals enrolled from five distinct community-based cohort studies conducted in the US and Europe, of whom fewer than 4% had HF, increasing plasma concentrations of natriuretic peptides were, along with increasing age, one of the strongest predictors of incident AF (22). In a Swedish cohort of patients free of cardiovascular disease, natriuretic peptides, particularly MR-proANP, but not other biomarkers (including mid-regional pro-adrenomedullin, cystatin C, and copeptin), predicted incident AF (23).

Other authors have shown that increasing plasma concentrations of natriuretic peptides are robust predictors of the recurrence of AF following ablation in patients with lone AF (24) or of recurrence in those with a history of paroxysmal AF (25). In a retrospective analysis from the Valsartan Heart Failure Trial (Val-HeFT), in which >4,000 patients had HFrEF and sinus rhythm, a BNP at study entry above the median value (97pg/ml) was the strongest predictor of AF occurrence (6.5% at 23 months) (12).

Although it is possible that raised levels of natriuretic peptides might promote atrial arrhythmias, it is more likely that higher plasma concentrations reflect advanced age and more advanced underlying cardiac and renal disease. In addition, higher natriuretic peptides are associated with atrial enlargement and dysfunction, often secondary to left ventricular dysfunction (26). We found a similar incidence of AF regardless of LVEF, similar to other reports (27). Our results also confirm that patients with heart failure and atrial fibrillation have a poorer outcome compared to those in sinus rhythm, regardless of LVEF (28).

We defined “incident AF” as documented AF on a 12-lead ECG at a follow up visit. We did not systematically investigate patients for paroxysmal AF using cardiac monitoring

because the clinical or therapeutic relevance of short, asymptomatic episodes of AF in patients with heart failure is not known and guidelines on heart failure do not recommend routine investigation (29). Some incident AF might have occurred shortly before death and would thus not have been reported. Other potential confounders, such time-dependent changes in medications or compliance to heart failure medications have not been assessed. Some patients were treatment-naïve at the time of referral or required adjustment in heart failure medications, which might have affected the risk of developing atrial fibrillation during their first year of follow-up. We included patients with either reduced LVEF below 45% or raised natriuretic peptides (NT-proBNP >220 ng/l) in this analysis, in agreement with ESC recommendation that were contemporary when the study was conceived. However, there is no universal agreement on the optimal cut-off of NT-proBNP to be used to diagnose, or to rule out, HF in the presence of a normal, or mildly reduced LVEF. The use of a lower cut-off to rule out HF (125ng/L), as suggested by the recent ESC-HF guidelines (18), led to the inclusion of patients with less severe cardiac dysfunction and a lower prevalence of AF amongst patients with HFpEF, reflecting the uncertainty about the diagnostic criteria for heart failure. However, predictors and the one-year incidence of AF remained similar for both HFrEF and HFpEF.

In conclusions, the prevalence of AF is high, especially in patients with HFpEF but its incidence is modest. This may be explained by a high concurrent onset of HF and AF. Greater age, a prior history of paroxysmal AF and increasing plasma concentrations of NT-proBNP, a marker of congestion, predict the risk of developing, or progressing to, persistent or permanent AF in patients with HF.

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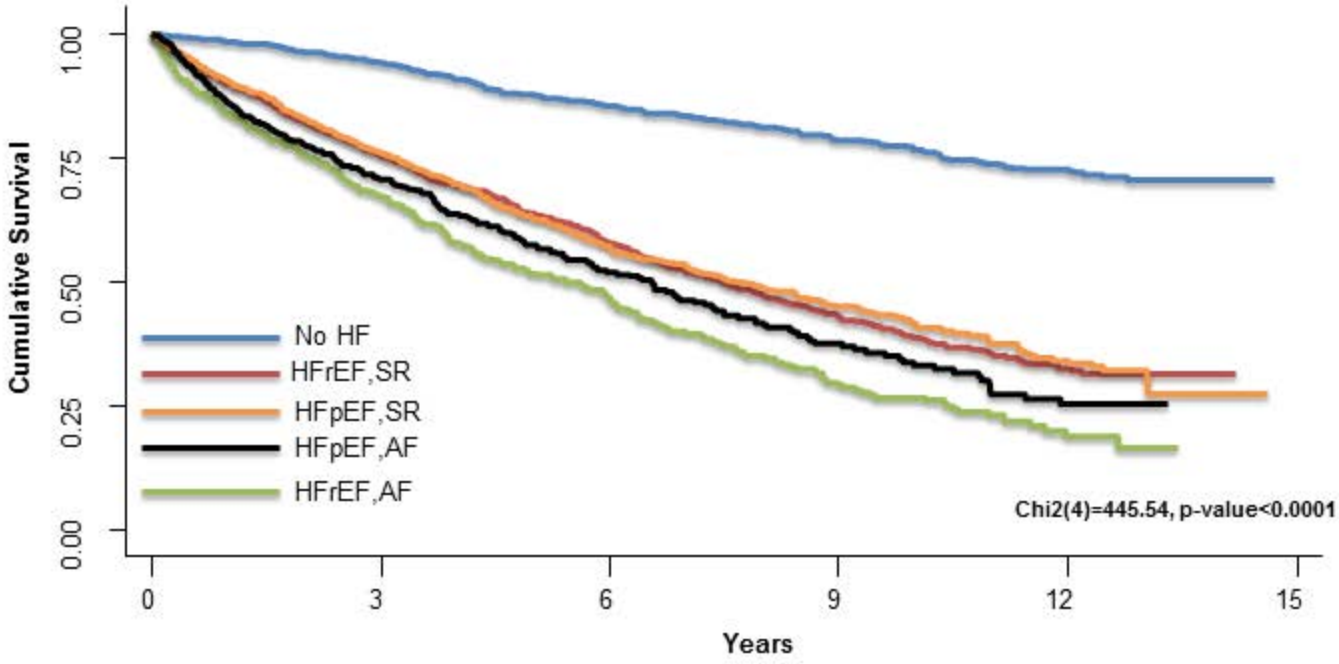
Legend to figures

Figure 1: Kaplan Meier curve for death from all causes. Patients with HFrEF and AF had the worst outcome (HR: 1.19, 95% CI 1.02-1.41, p=0.026 vs those with HFpEF and AF).

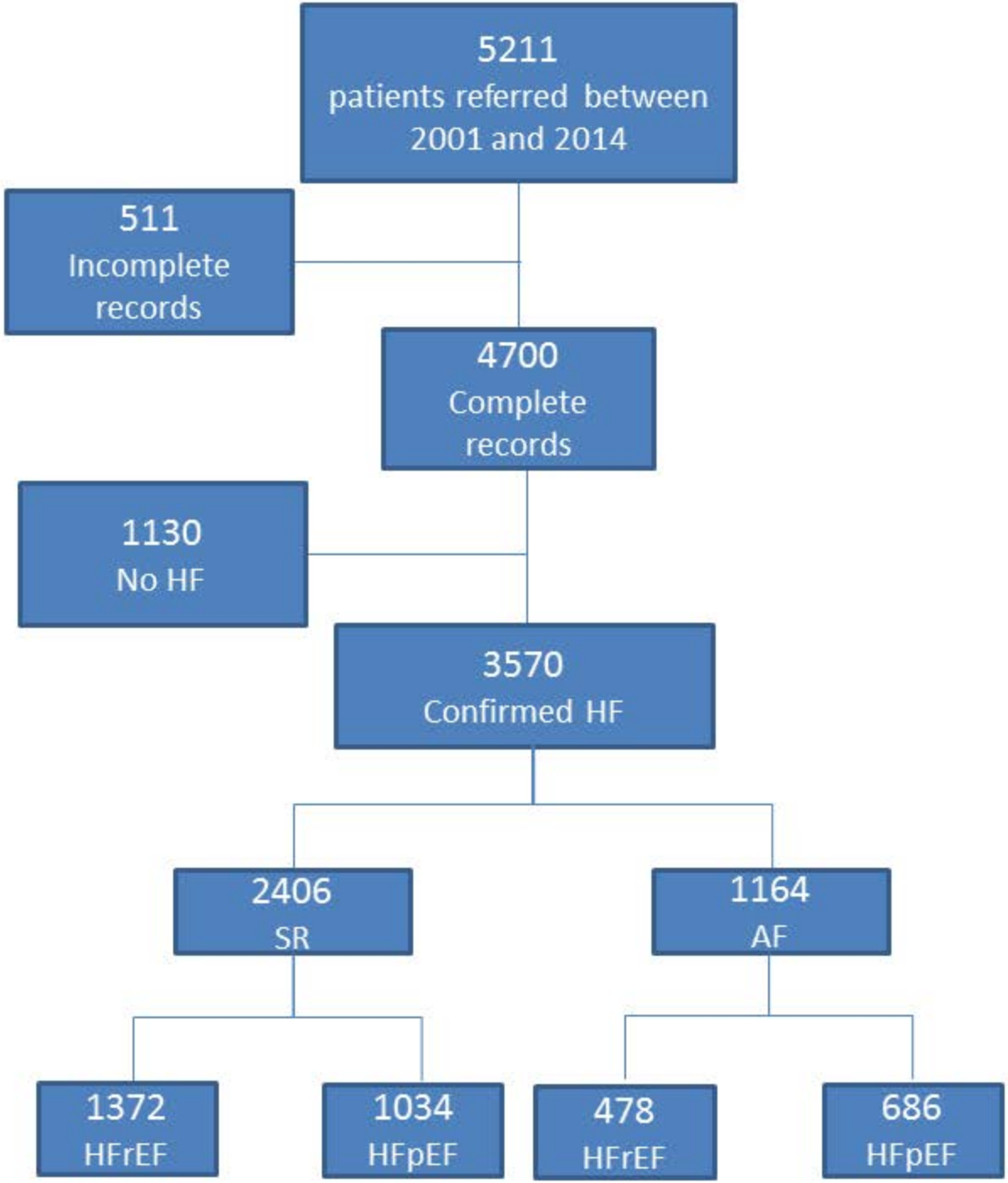
Figure 1 supplementary: Consort diagram showing the number of patients with suspected heart failure referred to our clinic between 2001 and 2014.

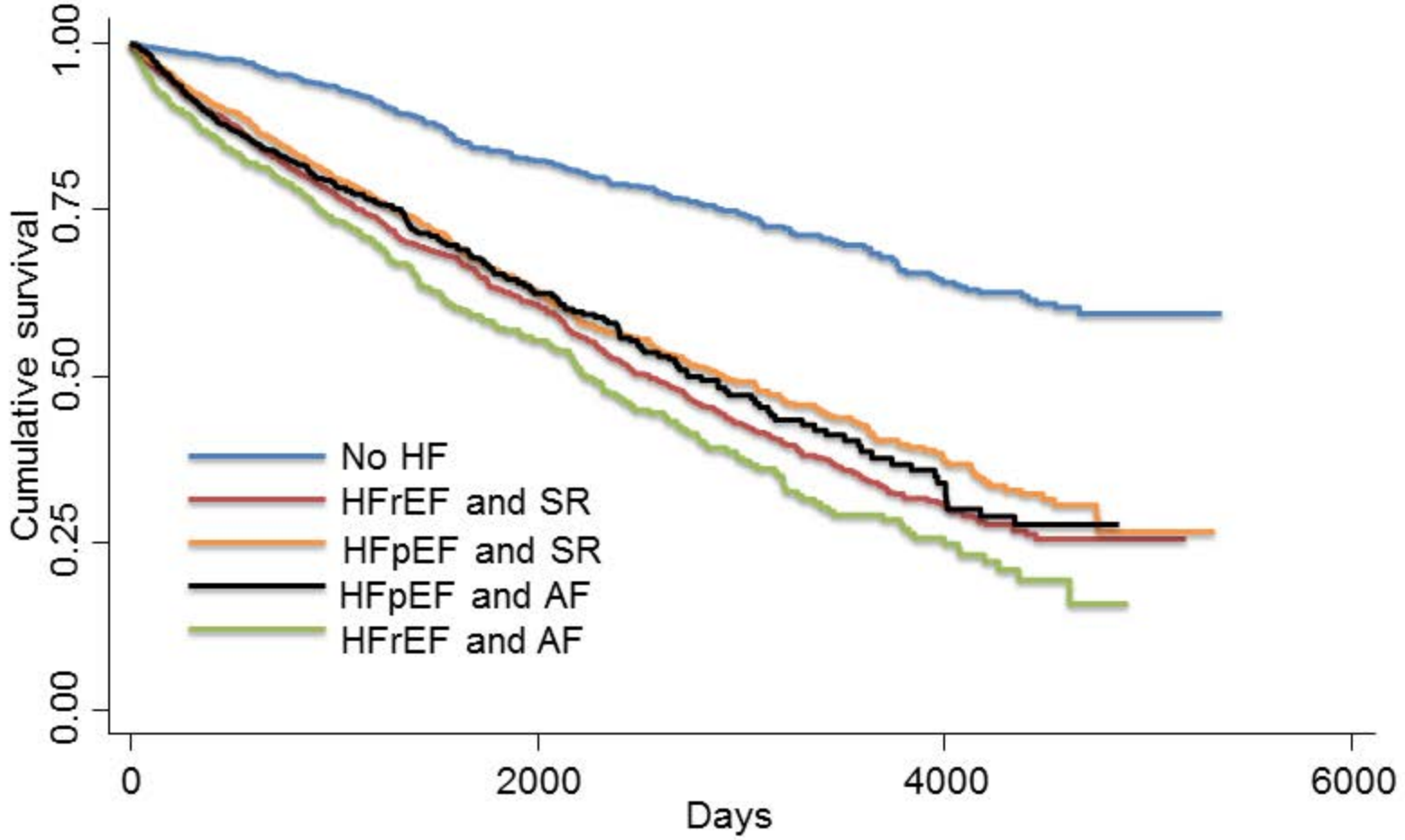
Figure 2 supplementary: Kaplan Meier curve for death from all causes, adjusted for age and sex. Patients with HFrEF and AF had the worst outcome (HR: 1.29, 95% CI 1.09-1.52, p=0.003 vs those with HFpEF and AF; adjusted for age and sex).



Number at risk

	1130	873	636	437	218	0
	1372	933	551	294	72	0
	1034	629	292	165	59	0
	686	392	144	64	25	0
	478	283	148	61	16	0


5211
patients referred between 2001 and 2014
511
Incomplete records
4700
Complete records
1130
No HF
3570
Confirmed HF
2406
SR
1164
AF
1372
HFrEF
1034
HFpEF
478
HFrEF
686
HFpEF


Cumulative survival
0.00
0.25
0.50
0.75
1.00
0
2000
4000
6000
Days
No HF
HFrEF and SR
HFpEF and SR
HFpEF and AF
HFrEF and AF

Variable	Missing	Heart Failure and Atrial Fibrillation (1164)	Heart Failure and Sinus Rhythm (2406)	p	HFrEF in Sinus Rhythm (1372)	HFpEF in Sinus Rhythm (1034)	p
Demographics							
Age (Years)	0	76 (70-82)	73 (65-79)	<0.001	71 (63-77)	76 (70-82)	<0.001
Men	0	774 (67%)	1483 (62%)	0.005	1002 (73%)	481 (47%)	<0.001
Body Mass Index (kg/m^2)	11	28 (25-32)	28 (25-32)	0.07	28 (24-31)	28 (25-32)	<0.001
Systolic Blood Pressure (mmHg)	11	136 (25)	139 (26)	<0.001	132 (24)	149 (26)	<0.001
Diastolic Blood Pressure (mmHg)	10	80 (16)	77 (14)	<0.001	76 (13)	78 (14)	<0.001
Heart Rate (bpm)	10	81 (20)	71 (15)	<0.001	72 (15)	70 (15)	<0.001
Diabetes Mellitus	0	278 (24%)	603 (25%)	0.444	326 (24%)	277 (27%)	0.090
Hypertension	0	629 (54%)	1238 (52%)	0.147	563 (41%)	675 (65%)	<0.001
Valvular Disease	0	192 (17%)	181 (8%)	<0.001	75 (6%)	106 (10%)	<0.001
Ischemic Heart Disease	0	483 (42%)	1425 (59%)	<0.001	956 (70%)	469 (45%)	<0.001
Previous TIA/Stroke	0	144 (12%)	163 (7%)	<0.001	103 (8%)	60 (6%)	0.100
Peripheral Vascular Disease	0	76 (7%)	179 (7%)	0.322	113 (8%)	66 (6%)	0.086
Paroxysmal Atrial Fibrillation	0	Not applicable	190 (8%)	Not applicable	116 (9%)	74 (7%)	0.242
NYHA Class I	0	174 (15%)	583 (24%)	<0.001	268 (20%)	315 (31%)	<0.001
NYHA Class II		571 (49%)	1156 (48%)		682 (50%)	474 (46%)	
NYHA Class III		399 (34%)	618 (26%)		386 (28%)	232 (22%)	
NYHA Class IV		20 (2%)	49 (2%)		36 (2%)	13 (1%)	
Blood results							
NT-proBNP (ng/L)	11	1936 (1057-3607)	833 (372-2119)	<0.001	1165 (474-3012)	587 (326-1288)	<0.001
Albumin (g/L)	233	37 (4)	38 (4)	0.001	38 (4)	37 (4)	0.002
Bilirubin (µmol/L)	243	16 (13-21)	13 (11-17)	<0.001	14 (12-18)	13 (10-15)	<0.001
Creatinine (µmol/L)	153	104 (86-130)	100 (82-128)	0.002	102 (86-128)	96 (79-125)	<0.001
Haemoglobin (g/dL)	157	13.4 (1.9)	13.1 (1.7)	<0.001	13.4 (1.7)	12.8 (1.7)	<0.001
K (mmol/L)	171	4.3 (4.0-4.6)	4.4 (4.1-4.7)	<0.001	4.4 (4.1-4.7)	4.3 (4.1-4.7)	0.001
Na (mmol/L)	151	138 (3)	138 (3)	0.894	138 (3)	138 (3)	0.584
Urea (mmol/L)	151	7.1 (5.4-9.8)	6.8 (5.2-9.2)	0.003	6.8 (5.3-9.2)	6.8 (5.2-9.2)	0.640
Thyroid-Stimulating Hormone (mU/L)	408	1.8 (1.2-2.8)	1.7 (1.1-2.5)	0.002	1.6 (1.0-2.5)	1.7 (1.1-2.6)	0.151
Medications[#]							

Loop diuretic	0	860 (74%)	1505 (63%)	<0.001	959 (70%)	546 (53%)	<0.001
Mineralocorticoid receptor antagonist	0	227 (20%)	525 (22%)	0.111	417 (30%)	108 (10%)	<0.001
ACE-I or ARB	0	812 (70%)	1743 (72%)	0.096	1115 (81%)	628 (61%)	<0.001
Beta-blockers	0	660 (57%)	1429 (59%)	0.126	906 (66%)	523 (51%)	<0.001
Echocardiography*							
Left Ventricular Ejection Fraction ≥55%	0	403 (35%)	618 (26%)	<0.001	0	618 (60%)	Not applicable
Left Ventricular Ejection Fraction: 46-54%		283 (24%)	416 (17%)		0	416 (40%)	
Left Ventricular Ejection Fraction: 36-45%		242 (21%)	658 (27%)		658 (48%)	0	
Left Ventricular Ejection Fraction: ≤35%		236 (20%)	714 (30%)		714 (52%)	0	
Left Atrial Diameter (cm)	431	4.7 (0.8)	4.0 (0.7)	<0.001	4.2 (1.7)	3.9 (0.7)	<0.001
Events							
Incident Atrial Fibrillation	0	Not applicable	291 (12%)	Not applicable	205 (15%)	86 (8%)	Not applicable
Incident Atrial Fibrillation at 1 year	0	Not applicable	62 (3%)	Not applicable	34 (3%)	28 (3%)	0.73

Table 1: Baseline characteristics of patients with HF, by diagnostic category and by heart rhythm. *Left Ventricular Ejection Fraction was measured (n=2013) or visually estimated. # Medications recorded at baseline prior to changes subsequent to initial referral.

Variable	Univariable analysis			Multivariable analysis LA included LA excluded		
	HR (95% CI)	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**
Age (1 Year increase)	1.03 (1.01-1.05)	17.69	<0.001	1.04 (1.02-1.05) 1.03 (1.02-1.05)	17.75 16.90	<0.001 <0.001
Male sex (vs female)	1.70 (1.31-2.21)	15.59	<0.001	1.64 (1.17-2.30) 1.98 (1.45-2.70)	8.29 18.75	0.004 <0.001
Body Mass Index (kg/m^2)	0.99 (0.98-1.02)	0.014	0.91			
Systolic Blood Pressure (mmHg)	0.99 (0.99-1.00)	6.34	0.012			
Diastolic Blood Pressure (mmHg)	0.99 (0.98-1.00)	6.23	0.013			
Heart Rate (bpm)	1.00 (1.00-1.01)	0.19	0.66			
Diabetes Mellitus (yes vs not)	1.12 (0.85-1.48)	0.68	0.41			
Hypertension (yes vs not)	0.89 (0.71-1.12)	0.99	0.32			
Valvular Disease (yes vs not)	1.13 (0.73-1.76)	0.29	0.59			
Ischemic Heart Disease (yes vs not)	1.40 (1.10-1.80)	7.16	0.007			
Previous TIA/Stroke (yes vs not)	0.95 (0.59-1.53)	0.05	0.95			
Peripheral Vascular Disease (yes vs not)	1.11 (0.71-1.75)	0.21	0.65			
Paroxysmal Atrial Fibrillation (yes vs not)	3.06 (2.26-4.13)	53.20	<0.001	2.52 (1.78-3.57) 2.62 (1.89-3.64)	27.18 33.28	<0.001 <0.001
NYHA class (III/IV vs I/II)	1.40 (1.08-1.81)	6.54	0.010			
LogNT-proBNP (ng/L)	2.39 (1.94-2.96)	64.69	<0.001	1.80 (1.34-2.42) 1.91 (1.46-2.50)	15.19 22.04	<0.001 <0.001
Albumin (g/l)	0.97 (0.94-1.00)	3.58	0.057			
Bilirubin (µmol/L)	1.03 (1.01-1.05)	13.53	<0.001			

Creatinine (µmol/L)	1.01 (1.00-1.01)	7.32	0.007			
Haemoglobin (g/dL)	0.94 (0.87-1.00)	3.28	0.070			
K (mmol/L)	1.03 (0.81-1.31)	0.06	0.81			
Na (mmol/L)	1.01 (0.97-1.05)	0.11	0.74			
Urea (mmol/L)	1.04 (1.02-1.06)	15.67	<0.001			
Thyroid-Stimulating Hormone (mU/L)	1.02 (0.99-1.04)	1.83	0.18			
HFrEF vs HFpEF	1.63 (1.27-2.09)	14.33	<0.001	1.44 (1.02-2.04) -	4.36 -	0.037 -
Left Atrial Diameter (cm)	1.78 (1.50-2.12)	42.86	<0.001	1.56 (1.28-1.89) -	20.17 -	<0.001 -

Table 2: Univariable and multivariable analysis for the incidence of atrial fibrillation in the overall population with heart failure. Two models were constructed, one including and one excluding left atrial diameter (available for 2085 patients, 87%). Variable included in the multivariable models were: age, sex, systolic blood pressure, diastolic blood pressure, ischaemic heart disease, paroxysmal atrial fibrillation, LogNT-proBNP, albumin, bilirubin, haemoglobin, urea, diagnostic category (HFrEF vs HFpEF) and left atrial diameter.

Quintile of NT-proBNP (range, ng/L)	**Patients with HFrEF with incident AF (per 1000 person-years), n**	**Hazard ratio (95% CI), p (vs Q1)**
Q1 (9-363)	14.44	1
Q2 (364-832)	25.51	1.80 (1.12-2.92); 0.016
Q3 (835-1652)	39.85	2.89 (1.82-4.58);<0.001
Q4 (1667-3780)	41.94	3.11 (1.93-4.99); <0.001
Q5 (3781-61888)	42.53	3.18 (1.93-5.25); <0.001
Quintile of NT-proBNP (range, ng/L)	**Patients with HFpEF with incident AF (per 1000 person-years), n**	**Hazard ratio (95% CI), p (vs Q1)**
Q1 (221-309)	8.95	1
Q2 (310-448)	9.22	1.03 (0.44-2.42); 0.948
Q3 (449-762)	15.28	1.64 (0.74-3.62); 0.223
Q4 (763-1573)	30.71	3.26 (1.59-6.69);0.001
Q5 (1575-35000)	41.57	4.29 (2.12-8.70);<0.001

Table 3. Risk of developing AF during follow-up according to NTproBNP quintiles in patients with HFrEF and HFpEF.

Variable	Missing values	No evidence of heart failure (n=1130)	Heart Failure (n=3570)	p
Demographics				
Age (Years)	0	68 (59-75)	74 (66-80)	<0.001
Men	0	582 (52%)	2257 (63%)	<0.001
Body Mass Index (kg/m^2)	16	29 (26-33)	27 (24-31)	<0.001
Systolic Blood Pressure (mmHg)	28	146 (21)	138 (26)	<0.001
Diastolic Blood Pressure (mmHg)	28	83 (12)	78 (14)	<0.001
Heart Rate (bpm)	12	71 (14)	74 (18)	<0.001
Diabetes Mellitus	0	275 (24%)	881 (25%)	0.816
Hypertension	0	667 (59%)	1867 (52%)	<0.001
Valvular Disease	0	41 (4%)	373 (10%)	<0.001
Ischemic Heart Disease	0	291 (26%)	1908 (53%)	<0.001
Previous TIA/Stroke	0	45 (4%)	307 (9%)	<0.001
Peripheral Vascular Disease	0	32 (3%)	255 (7%)	<0.001
Atrial Fibrillation	0	7 (1%)	1164 (33%)	<0.001
Paroxysmal Atrial Fibrillation	0	39 (4%)	191 (5%)	0.010
NYHA Class I	0	581 (52%)	757 (21%)	<0.001
NYHA Class II		400 (35%)	1727 (48%)	
NYHA Class III		140 (12%)	1017 (29%)	
NYHA Class IV		9 (1%)	69 (2%)	
Blood results				
NT-proBNP (ng/L)	11	88 (48-142)	1176 (502-2696)	<0.001
Albumin (g/l)	288	39 (3)	37 (4)	<0.001
Bilirubin (µmol/L)	300	13 (11-16)	14 (12-18)	<0.001
Creatinine (µmol/L)	184	82 (71-97)	102 (83-128)	<0.001
Haemoglobin (g/dL)	239	13.9 (1.4)	13.2 (1.8)	<0.001
K (mmol/L)	213	4.3 (4.0-4.5)	4.4 (4.1-4.7)	0.301
Na (mmol/L)	184	139 (3)	138 (3)	<0.001
Urea (mmol/L)	184	5.3 (4.3-6.5)	6.9 (5.3-9.4)	<0.001
Thyroid-Stimulating Hormone (mU/L)	592	1.6 (1.0-2.2)	1.7 (1.1-2.6)	<0.001
Medications[#]				

Loop diuretic	0	289 (26%)	2365 (66%)	<0.001
Mineralocorticoid receptor antagonist	0	35 (3%)	752 (21%)	<0.001
ACE-I or ARB	0	482 (43%)	2565 (72%)	<0.001
Beta-blockers	0	322 (29%)	2089 (59%)	<0.001
Echocardiography*				
Left Ventricular Ejection Fraction ≥55%	0	890 (79%)	1021 (29%)	<0.001
Left Ventricular Ejection Fraction: 46-54%		240 (21%)	699 (19%)	
Left Ventricular Ejection Fraction: 36-45%		0	900 (25%)	
Left Ventricular Ejection Fraction: ≤35%		0	950 (27%)	
Left Atrial Diameter (cm)	546	3.6 (0.6)	4.3 (0.8)	<0.001
Events				
Incident Atrial Fibrillation	0	30 (3%)	291 (12%)	Not applicable

Table 1 supplementary: Characteristics of patients at baseline, by diagnosis. *Left ventricular ejection fraction was measured (n=2660) or visually estimated. # Medications recorded at baseline prior to changes subsequent to initial referral.

Variable	HFrEF & Atrial Fibrillation (n=478)	HFpEF & Atrial Fibrillation (n=686)	p
Demographics			
Age (Years)	75 (68-81)	77 (71-82)	<0.001
Men	383 (80%)	391 (57%)	<0.001
Body Mass Index (kg/m^2)	28.0 (5.5)	29.8 (6.9)	<0.001
Systolic Blood Pressure (mmHg)	129 (24)	141 (24)	<0.001
Diastolic Blood Pressure (mmHg)	79 (16)	81 (15)	0.108
Heart Rate (bpm)	83 (21)	80 (19)	0.009
Diabetes Mellitus	105 (22%)	173 (25%)	0.200
Hypertension	219 (46%)	410 (60%)	<0.001
Valvular Disease	59 (12%)	133 (19%)	0.001
Ischemic Heart Disease	270 (57%)	213 (31%)	<0.001
Previous TIA/Stroke	70 (15%)	74 (11%)	0.049
Peripheral Vascular Disease	34 (7%)	42 (6%)	0.501
NYHA Class I	48 (10%)	126 (18%)	<0.001
NYHA Class II	223 (47%)	348 (51%)	
NYHA Class III	199 (41%)	200 (29%)	
NYHA Class IV	8 (2%)	12 (2%)	
Blood results			
NT-proBNP (ng/L)	2809 (1587-5051)	1507 (921-2651)	<0.001
Albumin (g/l)	37 (4)	38 (4)	0.067
Bilirubin (µmol/L)	18 (14-23)	16 (13-20)	<0.001
Creatinine (µmol/L)	111 (92-136)	99 (82-125)	<0.001
Haemoglobin (g/dL)	13.6 (1.8)	13.2 (1.8)	0.001
K (mmol/L)	4.3 (0.5)	4.3 (2.0)	0.373
Na (mmol/L)	138 (3)	138 (3)	0.566
Urea (mmol/L)	7.4 (5.5-10.4)	6.9 (5.3-9.4)	0.043
Thyroid-Stimulating Hormone (mU/L)	1.8 (1.2-2.9)	1.7 (1.1-2.8)	0.402
Medications#			
Loop diuretic	379 (79%)	481 (70%)	<0.001

Mineralocorticoid receptor antagonist	127 (27%)	100 (15%)	<0.001
ACE-I or ARB	374 (78%)	438 (64%)	<0.001
Beta-blockers	285 (60%)	375 (55%)	0.093
Echocardiography*			
Left Ventricular Ejection Fraction ≥55%	Not applicable	403 (35%)	Not applicable
Left Ventricular Ejection Fraction: 46-54%	Not applicable	283 (24%)	
Left Ventricular Ejection Fraction: 36-45%	242 (21%)	Not applicable	
Left Ventricular Ejection Fraction: ≤35%	236 (20%)	Not applicable	
Left Atrial Diameter (cm)	4.8 (4.4-5.2)	4.6 (4.2-5.1)	0.001

Table 2 supplementary: Baseline characteristics of patients with HF in AF, by diagnostic category. * Left Ventricular Ejection Fraction was measured (n=591) or visually estimated. # Medications recorded at baseline prior to changes subsequent to initial referral.

Variable	Univariable analysis			Multivariable analysis LA included LA excluded		
	HR (95% CI)	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**
Age (1 Year increase)	1.04 (1.02-1.05)	27.36	<0.001	1.04 (1.02-1.06)	14.86	<0.001
				1.03 (1.02-1.05)	13.66	<0.001
Male sex (vs female)	1.34 (0.96-1.88)	2.87	0.09	1.70 (1.09-2.64)	5.55	0.018
				1.86 (1.25-2.78)	9.40	0.002
Body Mass Index (kg/m^2)	0.99 (0.97-1.02)	0.27	0.60			
Systolic Blood Pressure (mmHg)	0.99 (0.99-1.00)	1.06	0.30			
Diastolic Blood Pressure (mmHg)	0.99 (0.99-1.00)	2.18	0.14			
Heart Rate (bpm)	1.00 (0.99-1.01)	0.01	0.91			
Diabetes Mellitus (yes vs not)	1.17 (0.84-1.61)	0.88	0.35			
Hypertension (yes vs not)	1.05 (0.79-1.39)	0.12	0.73			
Valvular Disease (yes vs not)	1.47 (0.85-2.53)	1.94	0.16			
Ischemic Heart Disease (yes vs not)	1.29 (0.94-1.76)	2.47	0.12			
Previous TIA/Stroke (yes vs not)	0.65 (0.34-1.23)	1.77	0.18			
Peripheral Vascular Disease (yes vs not)	0.77 (0.42-1.41)	0.73	0.39			
Paroxysmal Atrial Fibrillation (yes vs not)	3.07 (2.13-4.42)	36.26	<0.001	2.25 (1.46-3.47)	13.47	<0.001
				2.30 (1.50-3.53)	15.52	<0.001
NYHA class (III/IV vs I/II)	1.17 (0.86-1.59)	1.00	0.32			
LogNT-proBNP (ng/L)	2.04 (1.61-2.57)	33.90	<0.001	1.64 (1.19-2.27)	9.01	0.003

				1.66 (1.23-2.25)	10.85	0.001
Albumin (g/l)	0.95 (0.92-0.99)	6.68	0.010			
Bilirubin (µmol/L)	1.02 (1.00-1.04)	3.85	0.05			
Creatinine (µmol/L)	1.01 (1.00-1.01)	6.39	0.011			
Haemoglobin (g/dL)	0.88 (0.81-0.96)	9.40	0.002			
K (mmol/L)	1.19 (0.89-1.58)	1.34	0.25			
Na (mmol/L)	1.02 (0.97-1.06)	0.42	0.52			
Urea (mmol/L)	1.03 (1.01-1.05)	6.93	0.008			
Thyroid-Stimulating Hormone (mU/L)	1.02 (1.00-1.04)	4.38	0.036			
Left Atrial Diameter (cm)	1.56 (1.27-1.92)	17.45	<0.001	1.44 (1.14-1.81)	9.53	0.002
				-	-	-

Supplementary Table 3: Univariable and multivariable analysis for the incidence of atrial fibrillation in patients with heart failure and reduced ejection fraction (HFrEF). Two models were constructed, including or excluding left atrial diameter. Variables included in the multivariable models were: age, sex, paroxysmal atrial fibrillation, Log NTproBNP, bilirubin, haemoglobin, urea, thyroid-stimulating hormone**.**

Variable	Univariable analysis			Multivariable analysis LA included LA excluded		
	HR (95% CI)	**χ^2**	**p-value**	**HR (95% CI)**	**χ^2**	**p-value**
Age (1 Year increase)	1.02 (1.00-1.04)	2.59	0.11			
Male sex (vs female)	1.87 (1.21-2.89)	7.94	0.005	- 2.08 (1.30-3.31)	- 9.34	- 0.002
Body Mass Index (kg/m^2)	1.01 (0.98-1.05)	0.37	0.54			
Systolic Blood Pressure (mmHg)	0.99 (0.98-1.00)	0.75	0.39			
Diastolic Blood Pressure (mmHg)	0.99 (0.97-1.00)	2.53	0.11			
Heart Rate (bpm)	1.00 (0.99-1.01)	0.02	0.88			
Diabetes Mellitus (yes vs not)	0.94 (0.56-1.59)	0.05	0.83			
Hypertension (yes vs not)	0.86 (0.56-1.33)	0.44	0.51			
Valvular Disease (yes vs not)	0.91 (0.42-1.97)	0.06	0.81			
Ischemic Heart Disease (yes vs not)	1.28 (0.84-1.96)	1.33	0.25			
Previous TIA/Stroke (yes vs not)	1.78 (0.86-3.69)	2.42	0.12			
Peripheral Vascular Disease (yes vs not)	2.05 (1.03-4.11)	4.15	0.042			
Paroxysmal Atrial Fibrillation (yes vs not)	3.29 (1.94-5.60)	19.34	<0.001	2.89 (1.51-5.54) 3.50 (2.03-6.05)	10.32 20.23	0.001 <0.001
NYHA class (III/IV vs I/II)	1.82 (1.13-2.93)	6.09	0.014			
LogNT-proBNP (ng/L)	3.38 (2.12-5.39)	26.40	<0.001	2.60 (1.41-4.81) 2.86 (1.69-4.83)	9.36 15.36	0.002 <0.001

Albumin (g/l)	1.00 (0.94-1.06)	0.01	0.94			
Bilirubin (µmol/L)	1.04 (1.02-1.07)	8.22	0.004			
Creatinine (µmol/L)	1.00 (1.00-1.01)	0.18	0.67			
Haemoglobin (g/dL)	1.03 (0.89-1.18)	0.13	0.72			
K (mmol/L)	0.67 (0.44-1.04)	3.14	0.08			
Na (mmol/L)	1.00 (0.94-1.07)	0.01	0.95			
Urea (mmol/L)	1.05 (1.02-1.09)	8.17	0.004			
Thyroid-Stimulating Hormone (mU/L)	0.97 (0.87-1.08)	0.27	0.60			
Left Atrial Diameter (cm)	2.09 (1.52-2.89)	20.31	<0.001	1.71 (1.20-2.42)	8.99	0.003
				-	-	-

Supplementary table 4: Univariable and multivariable analysis for the incidence of atrial fibrillation in patients with heart failure and preserved ejection fraction (HFpEF). Two models were constructed, one including and one excluding left atrial diameter. Variable included in the multivariable models were: Sex, peripheral vascular disease, paroxysmal atrial fibrillation, NYHA IV/III vs I/II, Log NTproBNP, Bilirubin, K, Urea.

Variable	Multivariable analysis		
	HR (95% CI)	**χ^2**	**p-value**
Age (1 year increase)	1.03 (1.01-1.04)	15	<0.001
Male sex (vs female)	2.06 (1.51-2.78)	22	<0.001
Paroxysmal Atrial Fibrillation (yes vs not)	2.68 (1.93-3.71)	35	<0.001
LogNT-proBNP (ng/L)	2.05 (1.55-2.70)	26	<0.001
Bilirubin (µmol/L)	1.02 (1.00-1.04)	4	0.047

Supplementary table 5. Multivariable analysis for the incidence of atrial fibrillation (AF) in the overall population with heart failure, consistent with the 2016 European Society of Cardiology (ESC) guidelines. Two models were constructed, one including and one excluding (table above) left atrial diameter. Models included age, sex, systolic blood pressure, diastolic blood pressure, ischemic heart disease, history of paroxysmal atrial fibrillation, LogNT-proBNP, albumin, bilirubin, haemoglobin, urea, diagnostic category (HFrEF vs HFpEF). When added to the model, left atrial diameter independently predicted incident AF (HR (95% CI): 1.61 (1.33-1.95) per cm increase, χ^2 24, P<0.001), competing with bilirubin. Only variables independently associated with incident AF are shown.